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(54) Use of phytic acid or its salts for the prevention or treatment of hepatic diseases.

(57) Phytic acid or a salt thereof is known for pharmaceutical use: they are now administered orally as a treatment or preventive of hepatic diseases. Suitable non-toxic salts are metal salts and salts of an organic base, a basic amino acid or an organic ester residue.

The phytic acid or salt may be contained in a foodstuff, confectionary or a liquid. A daily dose of 1-100mg is suitable.

EP 0 349 143 A2

USE OF PHYTIC ACID OR ITS SALTS FOR THE PREVENTION OR TREATMENT OF HEPATIC DISEASES

The present invention relates to the use of a pharmaceutical composition for treating and preventing hepatopathies or hepatic diseases and to such an edible composition for improving hepatic functions, which contain phytic acid or at least a salt thereof as a pharmaceutically effective component.

Hepatopathies, especially those produced by acquired causes such as drug-induced and viral hepatopathies are more frequently found in the elderly and so are a sort of geriatric disease. However, juveniles of relatively tender age tend to suffer from such diseases by reason of irregular ingestion, insanitariness, maternal infection, sexual infection and the like which often result in a serious condition. Because of the unavailability of any decisive remedies for their treatment, there is still an urgent need to provide effective remedies and preventives.

On the other hand, phytic acids widely appear in plants as calcium and magnesium salts, sometimes a potassium salt. For instance, rice bran contains as high as 9.5 to 14.5% of phytic acid and provides a starting material for commercial phytic acid and myoinositol derived therefrom.

Phytic acid and its salt have been used for many purposes in pharmaceutical applications, calcium phytate has been used as a calcium augmentative, rice bran itself and sodium phytate as a preventive for calcium calculus, and potassium phytate for the treatment of hyper-calcemia and hyper-calciurea of sarcoidosis patients. They have also been utilized in various other fields as fermentative aids for brewing saké and wine, metal removers making use of the chelating action of phytic acid, antioxidants in the presence of iron and calcium ions and anticorrosives for metals.

However, it has not been reported until now that phytic acid and its salts may be used as a preventive and remedy for hepatopathies and edible compositions for enhancing hepatic functions.

Surprisingly, the inventors have now discovered that when orally administered during nutrition experiments, phytic acid serves to reduce body smells, inter alia, foul breath, perspiratory smell and urinous smell. In particular, further research studies of the removal of alcoholic breath by phytic acid has revealed that phytic acid takes part in the production and decomposition of alcohols, inter alia, aldehydic substances that are in vivo metabolites and has the property of detoxicating them (Japanese Patent Application No. 63-116338), and that phytic acid serves to protect the liver.

In view of the aforesaid findings, the present invention provides a remedy and preventive for hepatopathies and an edible composition for enhancing hepatic functions, which contain phytic acid or at least a salt thereof as an effective component.

The remedies or preventives according to the present invention are administrable and suitable for both humans and animals. The compositions used herein, and specific examples thereof may be the same as disclosed in our EPA 89302267.3 wherein phytic acid is used as an antidote to poisoning by drugs or alcohol.

The present invention will now be described with reference to the accompanying illustrative drawings, in which:-

Figures 1 to 3 are graphs illustrating changes-with-time in the concentration of alcohol in breath, as measured in Example 1;

Fig. 1 is a graph showing the results of testing with a male volunteer aged 26,

Fig. 2 a graph showing the results of testing with a male volunteer aged 27, and

Fig. 3 a graph showing the results of testing with a male volunteer aged 31.

In various preparations, phytates and their mixtures in a pH range of 6 to 8 may generally be selectively used depending upon the purposes of the pharmaceuticals and edible compositions because of their strong acidity.

The phytates usable in the present invention may include non-toxic metal salts as well as non-toxic salts with organic salts, basic amino acids and organic ester residues such as those represented by potassium phytate, sodium phytate, ammonium phytate, arginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamine phytate, triethanolamine phytate and glucamine phytate.

The number of moles of various bases required to adjust one mole of phytic acid pH to 8 is shown in Table 1.

Table 1

Bases	pH:	6.00	7.00	8.00
NaOH		7.34	8.21	8.94
KOH		7.34	8.23	8.94
LiOH		7.41	8.38	9.30
NH_4OH		7.61	8.55	9.45
$HOC_2HCH_2NH_2$		7.72	8.68	9.52
$(HOCH_2CH_2)_2NH$		7.54	8.45	9.31
$(HOCH_2CH_2)_3N$		7.20	8.53	12.1
N-Methylglucamine		7.62	8.49	9.25
L-Arginine		7.79	8.67	9.60
L-Lysine		8.01	8.98	10.0
L-Histidine		11.3	-	-

Phytic acid and its salt are so tasteless and odorless that their oral administration is easily achieved. Thus, the compositions provided by the present invention may be administered by mixing with drinking water for humans and animals or sprinkling over or blending with dishes or feed in the form of powders or granules.

Furthermore, it is also possible to add various flavorings or other ingredients to various phytates or their mixtures to prepare elixirs, capsules, granules, powders, tablets, syrups, dry syrups, troches, candies, limonadas, drinkable solutions, garlic flavorings and so on. It has been confirmed that phytic acid is very stable in such preparations.

A dosage of 1 to 100 mg/kg/day, calculated as phytic acid, of the compositions provided by the present invention may be suitable for humans, generally adults, although this depends upon the conditions of patients and the type of preparations.

To summarise, by use of the invention it is possible to easily obtain treatment and prevention of hepatopathies or enhancement of hepatic functions by the parenteral or oral administration of phytic acid and salts thereof.

Examples

The present invention will now be explained specifically but not exclusively with reference to the following examples.

Example 1

1: Pharmaceutical and Pharmacological Effect Tests

(1) Curative Effect Tests on Hepatopathy Models of Rats

Carbon Tetrachloride

One (1) mg/kg of carbon tetrachloride was administered to a male rat weighing about 200 g twice a week over ten weeks to induce hepatopathy.

How much the hepatopathy was cured was determined in a conventional manner by the measurement of the eluting enzymes GOT (Glutamate-oxaloacetate transaminase) and GPT (Glutamine-pyruvate transaminase) due to hepatic cytoclasis to calculate the therapeutic index.

After the inducement of hepatopathy, 10 mg/kg of potassium phytate was continuously administered to a group of five rats by the intraperitoneal route for 14 days (physiological saline was administered to a

control group) and blood was collected from the caudal veins for the measurement of GOT and GPT. As a consequence, a 45% or more increase in the therapeutic index was found. Vivisection also clearly indicated that the livers were ameliorated.

2: Effect upon the Amelioration of Drug Poisoning of Mice (Hepatic Function-Enhancing Tests)

Ten (10) mg/kg of potassium phytate was intraperitoneally administered to a group of six mice within 10 minutes of being anesthetized by the intraperitoneal injection of mg/kg of hexobarbital in order to compare arousal times. As a result, a 30% or more reduction in the arousal time was found. This appears to be due to the promoted decomposition and metabolism of the anesthetic in the liver since phytic acid has no hypersensitive or other substantial actions on the nerve system.

2. Clinical Tests

(1) Alcoholometry Testing (Metabolism Tests on the Enhancement of Hepatic functions)

After lunch, three male volunteers (age, weight:-26, 72 kg; 27, 56 kg; 31, 72 kg) were alcoholized by the administration of 300 ml of saké (15% ethanol) to measure the concentration of alcohol in breath with the lapse of time.

Two days later, the same subjects were alcoholized by the administration of saké, immediately followed by the administration of 105 mg/10 ml of potassium phytate (pH 7.0), for the measurement-with-time of the concentration of alcohol in breath.

Plotted in Figures 1 to 3 are the results, from which it was found that the concentration of alcohol in breath was reduced by the administration of phytic acid.

3. Organoleptic Testing

After drink, the drinkable solution of Preparation Example 1 was dosed to three panelists fond of alcohol. On inquiry of their drinking habit one month later, all the panelists answered that there was a decrease in the amount of their drinking because of shortened intoxication time, limited drunken sickness, a feeling of fullness and increased aversion to drinking.

In order to estimate significantly the effect of the preparations upon the enhancement of hepatic functions, it is required to collect and study a number of cases. However, the present preparation was organoleptically concluded as satisfactory, since none of the panelists said otherwise.

Example 2

1. Preparation Examples

Composition a

Twenty-nine (29) g of sodium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition b

Four hundred and twelve (412) g of potassium hydroxide and a suitable amount of refined water are

added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition c

One hundred and seventy-seven (177)g of lithium hydroxide and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition d

Five hundred and eighty-one (581) g of ethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition e

Nine hundred and seventy-nine (979) g of diethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition f

One thousand eight hundred and five (1805) g of triethanolamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 8.

Composition g

One thousand six hundred and fifty-seven (1657) g of N-methylglucamine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition h

One thousand five hundred and ten (1510) g of L-arginine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 7.

Composition i

One thousand seven hundred and fifty-three (1753) g of L-histidine and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid adjusted to pH 6.

Composition j

One hundred and sixteen (116) g of sodium hydroxide, 478 g of potassium hydroxide, 6.08 g of potassium chloride (as a dihydrate), 157 g of disodium hydrogen phosphate (as an anhydride) and a suitable amount of refined water are added to 660 g of phytic acid (as an anhydride) to obtain a liquid

adjusted to pH 9.

These compositions a to j may be powdered by crystallization or the addition of a vehicle.

These compositions a to j may also be formed into compositions in the form of liquids or powders, from which the preparations may be obtained.

Example 3

The composition j obtained in Example 2 was formed into the compositions below, from which various preparations were obtained.

Composition A for Preparations

Lactose is added to the composition j (containing 200 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition B for Preparations

Lactose is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition C for Preparations

Refined water is added to the composition j (containing 100 mg of phytic acid) to obtain a total of 1000 mg of a composition.

Composition D

Light silicic anhydride is added to the composition j (containing 200 mg of phytic acid), followed by drying, which gives a total of 1000 mg of a composition.

Production Examples of Preparations

Production Example (Elixir)

Composition C	100 g	(10 g calculated as phytic acid)
Compound orange extract	24 ml	
Ethanol	400 ml	
Glycerine	400 ml	
Refined water	Total: 1000 ml	

Predetermined amounts of the aforesaid components are uniformly mixed together to obtain a colorless and clear elixir preparation. A five-milliliter dosage of this elixir preparation contains 50 mg of phytic acid.

Production Example 2 (Capsule)

Composition A	200 mg	(40 mg calculated as phytic acid)
Lactose	20 mg	
Corn starch	38 mg	
Magnesium stearate	2 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together and packed in No. 2 capsules. One such capsule contains 40 mg of phytic acid.

Production Example 3 (Granule)

Composition A	600 mg	(120 mg calculated as phytic acid)
Lactose	140 mg	
Corn starch	250 mg	
Hydroxypropylcellulose	10 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then wet-granulated with water and ethanol into granules. One hundred and twenty (120) mg of phytic acid are contained in an one-gram dosage of such granules.

Production Example 4 (Powder)

The composition A is divided and heat-sealed in aluminium to obtain wrappers each of 1.5g of powder.

Production Example 5 (Tablet)

Composition A	100 mg	(20 mg calculated as phytic acid)
Corn starch	19 mg	
Crystalline cellulose	30 mg	
Magnesium stearate	1 mg	

Predetermined amounts of the aforesaid components are uniformly mixed together, and the mixture is then compressed into tablets each of 7 mm in diameter and 150 mg in weight. One such tablet contains 20 mg of phytic acid.

Production Example 6 (Syrup)

Composition C	50 g	(5 g calculated as phytic acid)
White sugar	300 g	
D-sorbitol(70%)	250 g	
Methyl p-oxybenzoate	0.3 g	
Propyl p-oxybenzoate	0.15 g	
Sodium citrate	10 g	
Perfume	1.5 g	
Refined water	Total: 1000 ml	

Predetermined amounts of the aforesaid components are dissolved and mixed together into a colorless and clear syrup. One hundred (100) mg of phytic acid is contained in a twenty-milliliter dosage of this syrup.

Production Example 7 (Dry syrup)

Composition B	100 mg	(10 mg calculated as phytic acid)
Sodium citrate	2.4 mg	
Citric anhydride	2.2 mg	
Tragacanth powders	2.7 g	
White sugar	suitable amount	
Hydroxypropylcellulose	3.0 mg	
Perfume	slight amount	
Perfume	slight amount	

Predetermined amounts of the aforesaid components are uniformly mixed together, and are then wet-granulated with water and ethanol into a dry syrup. An one (1)-gram dosage of this syrup contains 10 mg of phytic acid.

Production Example 8 (Troche)

Composition A	100 mg	(20 mg calculated as phytic acid)
White sugar	870 mg	
Lactose	20 mg	
Magnesium stearate	10 mg	

Of the aforesaid components the composition A and white sugar are uniformly mixed together in the respective amounts of 100 g and 870 g, and are then wet-granulated with water and ethanol, followed by drying at a temperature of lower than 35°C. Added to the dried product are 20 g of lactose and 10 g of magnesium stearate to obtain troches each of 15 mm in diameter and 1 g in weight. One such troche contains 20 mg of phytic acid.

Production Example 9 (Candy)

Composition B	100 mg	(10 mg calculated as phytic acid)
White sugar	2400 mg	
Starch syrup	1500 mg	
Perfume	slight amount	

Of the aforesaid components, 240 g of white sugar and 150 g of starch syrup are mixed with 100 g of refined water. After melting by heating, the mixture is sieved for the removal of foreign matters. The resulting liquid is concentrated under pressure with the application of heat for dehydration to prepare a starch syrup dough having a moisture content of 2 to 3 % at 130 to 150 °C. Added to this dough are 10 g of the composition B and a slight amount of perfume, and the product is molded to obtain candies each of 4 g in weight. Each candy contains 10 mg of phytic acid.

Production Example 10 (Magnesium Citrate Oral Solution)

Composition C	3 g	(300 mg calculated as phytic acid)
Syrup	2.5 ml	
Refined water	Total: 30 ml	

Predetermined amounts of the aforesaid components are uniformly mixed together into "limonada". A thirty (30)-milliliter dosage of such limonadas contains 300 mg of phytic acid.

Production Example 11 (Granules)

Composition D	500 mg	(100 mg calculated as phytic acid)
Garlic powders	750 mg	
Lactose	suitable amount	

Predetermined amounts of the aforesaid components are uniformly mixed together, and are then wet-granulated with water and ethanol into granules. One hundred (100) mg of phytic acid is contained in an 1.5-gram dosage of such granules.

Production Example 12 (Drinkable Solution)

Composition C	1 g	(100 mg calculated as phytic acid)
Mel	0.5 g	
White sugar	2.0 g	
Citric acid	suitable amount	
Sodium citrate	suitable amount	
Peppermint	slight amount	
Refined water	suitable amount	

Predetermined amounts of the aforesaid components were uniformly mixed together into a colorless and clear internal liquid preparation. A thirty (30)-milliliter dosage of this liquid preparation contains 100 mg of phytic acid.

Production Example 13 (Garlic Flavoring)

Composition D	0.285 g	(0.1 g calculated as phytic acid)
Avicel (Cellulose microcrystalline)	0.18 g	
Garlic powders	0.75 g	
Light silicic anhydride	0.256 g	
Corn starch	suitable amounts	

Predetermined amounts of the aforesaid components are granulated by a conventional method.

Stability Testing

The preparations according to Production Examples 1 to 12 were subjected to stability testing to measure the amount of residual phytic acid. The results are set forth in Table 2.

Table 2

Amounts of Residual Phytic Acid in the Stability Testing of the Preparations According to the Production Examples (% with respect to the specified contents)			
Samples	Storage Vessels	At the beginning of Storage	After 3 weeks at 60° C
P.Ex.1A*	Glass Bottle	100.5	101.2
P.Ex.2B*	PTP	101.4	99.4
P.Ex.3C*	Aluminium Wrapper	100.1	100.0
P.Ex.4D*	"	100.9	102.1
P.Ex.5E*	PTP	99.2	99.8
P.Ex.6F*	Glass Bottle	102.1	100.3
P.Ex.7G*	Aluminium Wrapper	100.6	100.1
P.Ex.8H*	Aluminium SP	99.7	100.5
P.Ex.9I*	Aluminium Bag	99.9	99.2
P.Ex.10J*	Glass Bottle	102.1	100.9
P.Ex.11K*	Aluminium Wrapper	100.3	100.1
P.Ex.12L*	Glass Bottle	100.1	99.8

A*: Elixir,
B*: Capsule,
C*: Granule,
D*: Powder,
E*: Tablet,
F*: Syrup,
G*: Dry Syrup,
H*: Troche,
I*: Candy,
J*: Limonada,
K*: Granule,
L*: Drinkable Solution.

Claims

1. Use of phytic acid and/or a salt thereof for the manufacture of a medicament for the prevention or treatment of hepatic diseases or improvement of hepatic function.

2. Use, as claimed in Claim 1, wherein the hepatic diseases are drug-induced or viral hepatic diseases.

3. Use, as claimed in Claim 1 or 2, wherein the medicament is a composition in a form suitable for oral administration.

4. Use, as claimed in any preceding claim, wherein the salt of phytic acid is a non-toxic metal salt, or a non-toxic salt with an organic base, a basic amino acid or an organic ester residue.

5. Use, as claimed in Claim 4, wherein the salt of phytic acid is selected from potassium phytate, sodium phytate, ammonium phytate, arginine phytate, ornithine phytate, lysine phytate, histidine phytate, monoethanolamine phytate, diethanolamine phytate, triethanolamine phytate and glucamine phytate.

6. Use, as claimed in any preceding claim, wherein 1 to 100mg of phytic acid and/or a salt thereof are orally administered per day.

FIG. 1

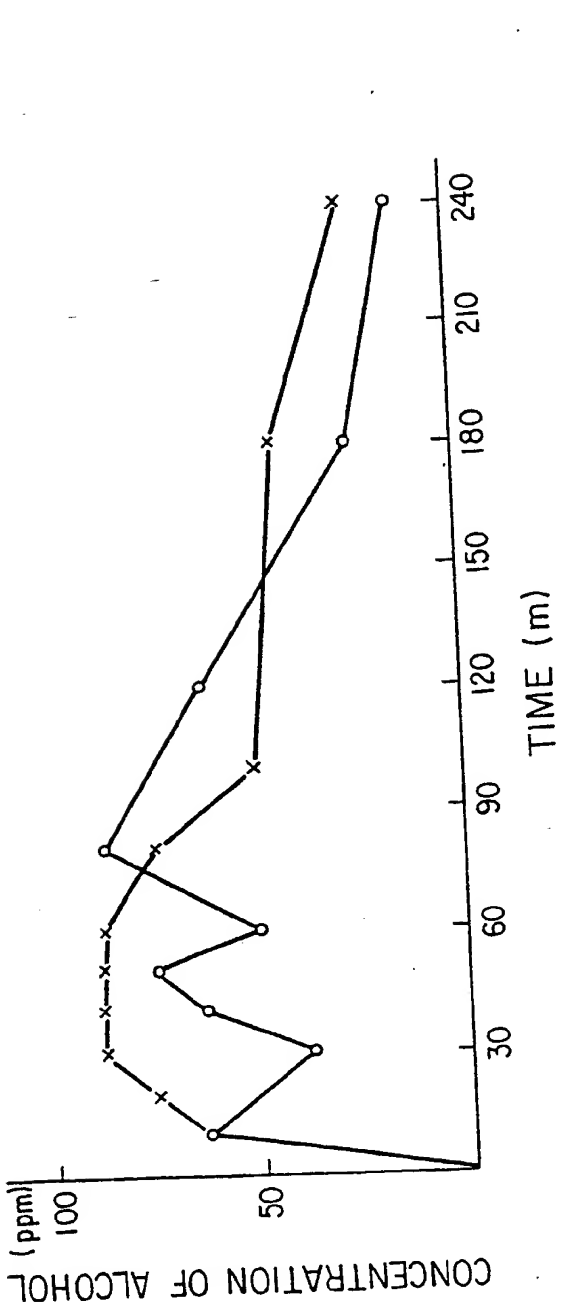

MALE VOLUNTEER 26, 72kg
× SAKE 300mℓ
o SAKE 300mℓ+POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL (ppm)
100
50
30
60
90
120
150
180
210
240
TIME (m)

FIG. 2

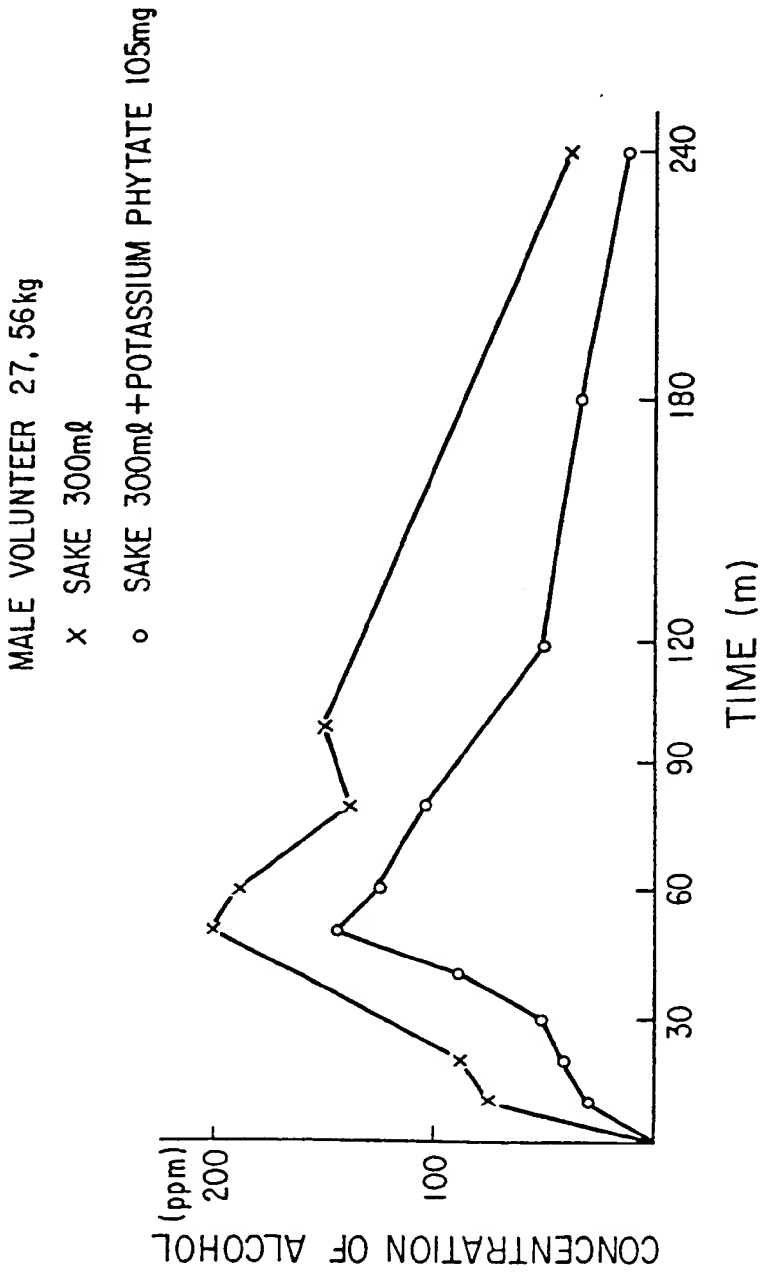
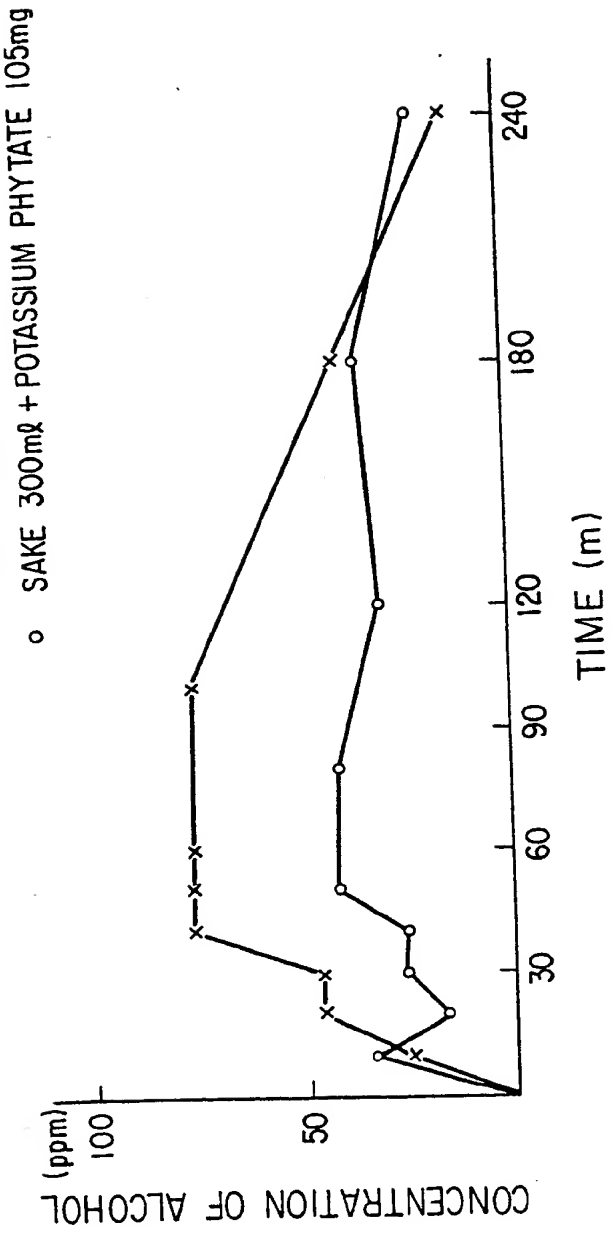

MALE VOLUNTEER 27, 56kg
× SAKE 300mℓ
○ SAKE 300mℓ+POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL (ppm)
200
100
30
60
90
120
180
240
TIME (m)

FIG. 3


MALE VOLUNTEER 31, 72kg
× SAKE 300mℓ
o SAKE 300mℓ + POTASSIUM PHYTATE 105mg
CONCENTRATION OF ALCOHOL
(ppm)
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50
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EUROPEAN SEARCH REPORT

Application Number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	PATENT ABSTRACTS OF JAPAN, vol. 8, no. 110 (C-224)[1547], 23rd May 1984; & JP-A-59 25 677 (KEI AI KAGAKU K.K.) 09-02-1984 * Abstract * ---	1-6	A 61 K 31/66
A	JOURNAL OF VITAMINOLOGY, vol. 16, no. 1, 1970, pages 75-79; A. KOTAKI et al.: "Studies on myoinositol. V. Effect of myoinositol on the prevention of fatty liver induced by orotic acid" * Page 76, left-hand column, lines 6-10 - right-hand column, lines 16-19; page 78, left-hand column, lines 10-13 * ---	1-6	
A	JOURNAL OF VITAMINOLOGY, vol. 17, 1971, pages 112-116; I. NISHIGAKI et al.: "Studies on myoinositol. VII. Removal of deposited fats from dietary fatty liver" * Page 112, left-hand column, line 8 - right-hand column, line 1; page 113, left-hand column, lines 5-9; page 114, left-hand column, lines 13-25 * ---	1-6	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K
A	J. NUTR., vol. 107, no. 10, October 1977, pages 1871-1883; L.E. BURTON et al.: "Characterization of the lactation-dependent fatty liver in myo-inositol deficient rats" * The whole document * --- -/-	1-6	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17-07-1990	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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EUROPEAN SEARCH REPORT

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	ANN. N.Y. ACAD. SCI., vol. 165, no. 2, 1969, pages 710-725; H. YAGI et al.: "The effect of massive doses of Myo-inositol on hepatic phospholipid metabolism" * Page 724, lines 1-9 *	1-6	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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